General

Guideline Title

Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review).

Bibliographic Source(s)

England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, Asbury AK, Szigeti K, Lupski JR, Latov N, Lewis RA, Low PA, Fisher MA, Herrmann DN, Howard JF Jr, Lauria G, Miller RG, Polydefkis M, Sumner AJ. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Neurology. 2009 Jan 13;72(2):185-92. [37 references] PubMed

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology reaffirmed the currency of this guideline in 2013.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Role of Laboratory Testing in the Evaluation of Polyneuropathy

Conclusions

Screening laboratory tests are possibly useful in determining the cause of distal symmetric polyneuropathy (DSP), but the yield varies depending upon the particular test (Class III). The tests with the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Class III). Patients with distal symmetric sensory polyneuropathy have a relatively high prevalence of diabetes or prediabetes (impaired glucose tolerance), which can be documented by blood glucose or glucose tolerance testing (GTT) (Class III).

Recommendations

Screening laboratory tests may be considered for all patients with DSP (Level C). Although routine screening with a panel of basic tests is often performed (see table e-1 in the original guideline document), those tests with the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C). When routine blood

glucose testing is not clearly abnormal, other tests for prediabetes (impaired glucose tolerance) such as a GTT may be considered in patients with distal symmetric sensory polyneuropathy, especially if it is accompanied by pain (Level C).

Although there are no control studies (Level U) regarding when to recommend the use of other specific laboratory tests, clinical judgment correlated with the clinical picture will determine which additional laboratory investigations (see table e-2 in the original guideline document) are necessary.

Role of Genetic Testing in the Evaluation of Polyneuropathy

Conclusions

Genetic testing is established as useful for the accurate diagnosis and classification of hereditary polyneuropathies (Class I). For patients with a cryptogenic polyneuropathy who exhibit a classic hereditary neuropathy phenotype, routine genetic screening may be useful for Charcot-Marie-Tooth 1A (CMT1A) duplication/ deletion and *Cx32* mutations in the appropriate phenotype (Class III). Further genetic testing may be considered guided by the clinical question. There is insufficient evidence to determine the usefulness of routine genetic screening in cryptogenic polyneuropathy patients without a classic hereditary neuropathy phenotype.

Recommendations

Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A). Genetic testing may be considered in patients with a cryptogenic polyneuropathy and classic hereditary neuropathy phenotype (Level C). There is insufficient evidence to support or refute the usefulness of routine genetic testing in cryptogenic polyneuropathy patients without a classic hereditary phenotype (Level U).

Clinical Context

To achieve the highest yield, the genetic testing profile should be guided by the clinical phenotype, inheritance pattern (if available), and electrodiagnostic (EDX) features (demyelinating vs. axonal). See the figure in the original guideline document for guidance.

Definitions:

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if: 1) all criteria are met, (2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

Classification of Evidence for Studies of Diagnostic Accuracy

Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III: A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion, or a case report.

Clinical Algorithm(s)

A clinical algorithm for use in the evaluation of suspected heredity neuropathies is provided in the original guideline document.

Scope

Disease/Condition(s)

Distal symmetric polyneuropathy (DSP)

Guideline Category

Diagnosis

Evaluation

Screening

Technology Assessment

Clinical Specialty

Internal Medicine

Medical Genetics

Neurology

Physical Medicine and Rehabilitation

Intended Users

Patients

Physicians

Guideline Objective(s)

To provide evidence-based guidelines regarding the role of laboratory and genetic tests in the evaluation of distal symmetric polyneuropathy (DSP)

Target Population

Patients with distal symmetric polyneuropathy (DSP)

Interventions and Practices Considered

Laboratory testing, including blood glucose, serum B12 with metabolites, serum protein immunofixation electrophoresis, and glucose tolerance testing (GTT)
Genetic testing

Major Outcomes Considered

The usefulness and accuracy of laboratory and genetic testing in the evaluation of distal symmetric polyneuropathy (DSP)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2009 Guideline

The literature search included OVID MEDLINE (1966 to March 2007), OVID Excerpta Medica (EMBASE; 1980 to March 2007), and OVID Current Contents (2000 to March 2007). The search included articles on humans only and in all languages. The search terms selected were peripheral neuropathy, polyneuropathy, and distal symmetric polyneuropathy. These terms were cross-referenced with the terms laboratory test, diagnosis, electrophysiology, and genetic testing.

Panel experts were asked to identify additional articles missed by the initial search strategy. Further, the bibliographies of the selected articles were reviewed for potentially relevant articles.

2013 Reaffirmation

The guideline developer searched Medline, EMBASE, and Current Contents for studies published between 2009 and 2013 using the following search terms: peripheral neuropathy, polyneuropathy, and distal symmetric polyneuropathy. These terms were cross-referenced with the terms laboratory test, diagnosis, electrophysiology, and genetic testing.

Number of Source Documents

450 articles were reviewed and classified.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Studies of Diagnostic Accuracy

Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III: A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by

different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion, or a case report.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Subgroups of committee members reviewed the titles and abstracts of citations identified from the original searches and selected those that were potentially relevant to the evaluation of polyneuropathy. Articles deemed potentially relevant by any panel member were also obtained.

Each potentially relevant article was subsequently reviewed in entirety by at least three panel members. Each reviewer graded the risk of bias in each article by using the diagnostic test classification-of-evidence scheme (see "Rating Scheme for the Strength of the Evidence). In this scheme, articles attaining a grade of Class I are judged to have the lowest risk of bias, and articles attaining a grade of Class IV are judged to have the highest risk of bias. Disagreements among reviewers regarding an article's grade were resolved through discussion. Final approval was determined by the entire panel.

Methods Used to Formulate the Recommendations

Other

Description of Methods Used to Formulate the Recommendations

2009 Guideline

The Polyneuropathy Task Force developed a set of clinical questions relevant to the evaluation of distal symmetric polyneuropathy (DSP), and subcommittees were formed to address each of these questions.

2013 Reaffirmation

The American Academy of Neurology (AAN) assesses their clinical practice guidelines every 2 years to determine whether new literature has been published that would warrant an update. The following steps are taken:

- Biennial correspondence is sent to all authors and the facilitator.
- An updated literature search and a review of methodological soundness are performed by a Guideline Development Subcommittee (GDS) member. (Note: The search should specifically seek to identify new evidence that would change the conclusions in the systematic review or recommendations in the CPG.)

All documents biennially reviewed by the GDS that don't require an update are reaffirmed. See the AAN Clinical Practice Guideline Process Manual for additional information.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if: 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.)

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN), the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the Practice Guidelines Committee of the American Academy of Physical Medicine and Rehabilitation (AAPM&R) reviewed and approved a draft of the article. The draft was next sent to members of the AAN, AANEM, and AAPM&R for further review and then to *Neurology*® for peer review. Boards of the AAN, AANEM, and AAPM&R reviewed and approved the final version of the article. At each step of the review process, external reviewers' suggestions were explicitly considered. When appropriate, the expert panel made changes to the document.

The guideline was approved by the QSS on November 10, 2007; by the AAN Practice Committee on January 20, 2008; by the Neuromuscular Guidelines Steering Committee on April 22, 2008; by the AAN Board of Directors on August 20, 2008; by the AANEM Board of Directors on May 1, 2008; and by the AAPM&R Board of Governors on April 7, 2008.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of laboratory and genetic testing to evaluate patients with distal symmetric polyneuropathy (DSP)

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

The diagnosis and evaluation of polyneuropathy is complex. The practice parameter is not intended to replace the clinical judgment of experienced physicians in the evaluation of polyneuropathy. The particular kinds of tests utilized by a physician in the evaluation of polyneuropathy depend upon the specific clinical situation and the informed medical judgment of the treating physician.
This statement is provided as an educational service of the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and American Academy of Physical Medicine and Rehabilitation (AAPM&R). It is based upon an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific test or procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN, AANEM, and AAPM&R recognize that specific care decisions are the prerogative of the patient and physician caring for the patient, based on all of the circumstances involved.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

Wall Poster

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, Asbury AK, Szigeti K, Lupski JR, Latov N, Lewis RA, Low PA, Fisher MA, Herrmann DN, Howard JF Jr, Lauria G, Miller RG, Polydefkis M, Sumner AJ. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Neurology. 2009 Jan 13;72(2):185-92. [37 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2009 Jan (reaffirmed 2013 Jan)

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

American Academy of Physical Medicine and Rehabilitation - Medical Specialty Society

American Association of Neuromuscular and Electrodiagnostic Medicine - Medical Specialty Society

Source(s) of Funding

American Academy of Neurology (AAN)

Guideline Committee

The Polyneuropathy Task Force

Composition of Group That Authored the Guideline

Task Force Members: J.D. England, MD; G.S. Gronseth, MD, FAAN; G. Franklin, MD; G.T. Carter, MD; L.J. Kinsella, MD; J.A. Cohen, MD; A.K. Asbury, MD; K. Szigeti, MD, PhD; J.R. Lupski, MD, PhD; N. Latov, MD; R.A. Lewis, MD; P.A. Low, MD; M.A. Fisher, MD; D.N. Herrmann, MD; J.F. Howard, Jr, MD; G. Lauria, MD; R.G. Miller, MD; M. Polydefkis, MD, MHS; A.J. Sumner, MD

Financial Disclosures/Conflicts of Interest

The American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and American Academy of Physical Medicine and Rehabilitation (AAPM&R) are committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN, AANEM, and AAPM&R keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN, AANEM, and AAPM&R limit the participation of authors with substantial conflicts of interest. The AAN, AANEM, AAPM&R forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been

reviewed by at least three AAN committees, AANEM and AAPM&R committees, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com .

J.D.E. holds financial interests in Pfizer and has received research support from Wyeth and Pfizer. G.S.G. has received speaker honoraria from Pfizer, GlaxoSmithKline, and Boehringer Ingelheim and served on the IDMC Committee of Ortho-McNeil. He estimates that <2% of his clinical effort is spent on EMG and EEG. G.F., A.K.A., and K.S. have nothing to disclose. G.T.C estimates that 30% of his clinical effort is spent on EMG. J.A.C. has received speaker honoraria from Athena Diagnostics and estimates that 40% of his clinical effort is spent on EMG/NCS, 10% on autonomic testing, and 10% on botulinum toxin injections. L.J.K. has received speaker honoraria from American Medical Seminars, Cross Country Education, Therapath Laboratories and CME, LLC, and holds equity in Passnet Air Ambulance. He estimates 25% of his clinical effort is spent on NCS/EMG, 4% on skin biopsy for nerve fiber counting, and 8% on autonomic studies, and has received payment for expert testimony in legal proceedings. J.R.L. holds financial interests in Athena Diagnostics and has received research funding from NIH/NEI, NIH/NIDCR, Charcot-Marie-Tooth Association, and the March of Dimes. N.L. serves as a consultant for Talecris Biopharmaceuticals and Quest Diagnostics, receives royalties from Athena Diagnostics, and holds equity and is a partner in Therapath LLC. He is the Medical and Scientific Director for the Neuropathy Association, estimates that <1% of his clinical effort is spent on skin biopsy, and has received research support from Talecris Biotherapeutics. R.A.L. has consulted for Talecris and has received research funding from MDA, Baxter Pharmaceuticals, and CMTA. He estimates that 33% of his clinical effort is spent on electromyography. He has received payment for expert testimony regarding the use of IVIg in CIDP and neuropathic pain after breast reduction. P.A.L. estimates 25% of his clinical effort is spent on autonomic reflex screening. D.H. has received research funding from NIH, Astellas Pharmaceutical Company, and MDA/ CMT Association. He estimates that 25% of his clinical effort is spent on EMG and 20% on skin biopsies. J.F.H. holds financial interests in FEMI, Johnson & Johnson, Pfizer, and General Electric. He estimates that 40% of his clinical effort is spent on EMG/NCS. G.L. holds financial interests in GlaxoSmithKline and Formenti-Grunenthal. In addition, he has received research funding from Pfizer, Formenti-Grunenthal, Italian Ministry of Health, and Regione Lombardia. He estimates that 25% of his clinical effort is spent in an outpatient pain center, 25% on out- and inpatient clinical examination, 25% on skin biopsy examination, and 25% on research. R.G.M. holds financial interests in Celgene, Knopp Neurosciences, Medivation, Teva Neuro, Taiji Biomedicals, and Translational Genomics. M.P. serves on the scientific advisory board of GSK, the editorial board of Journal of the Peripheral Nervous System, the speakers' bureau of Pfizer and participated in the Joslin diabetes CME programs. He has received research funding from Astellas Pharma and Mitsubishi Pharma and reads clinical skin biopsies, runs an EMG lab, and cares for patients with peripheral nerve diseases. A.J.S. has received payment for expert testimony in the possible neurotoxic injury of the peripheral nerve.

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology reaffirmed the currency of this guideline in 2013.

Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site .

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 201 Chicago Avenue South, Minneapolis, MN 55415.

Availability of Companion Documents

The following are available:

- The role of laboratory and genetic testing in diagnosing distal symmetric polyneuropathy. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2008. 2 p. Available in Portable Document Format (PDF) from the AAN Web site .
- Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory, genetic, and autonomic testing; nerve biopsy; and skin biopsy (an evidence-based review). Case study and coding. St. Paul (MN): American Academy of Neurology. 2008. 6 p. Available from the AAN Web site .

- Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory, genetic, and autonomic testing; nerve biopsy; and skin biopsy (an evidence-based review) Slide presentation. St. Paul (MN): American Academy of Neurology. 2008. 59 p. Available from the AAN Web site .
- Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory, genetic, and autonomic testing; nerve biopsy; and skin biopsy (an evidence-based review). Wall poster. St. Paul (MN): American Academy of Neurology. 2009. 1 p. Available from the AAN Web site .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site .

Patient Resources

The following is available:

- Distal symmetric polyneuropathy. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2008. 2 p. Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on February 25, 2009. The information was verified by the guideline developer on May 12, 2009. The currency of the guideline was reaffirmed by the developer in 2013 and this summary was updated by ECRI Institute on May 27, 2015.

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